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## CLAIMS

I claim:

1. A method of increasing absorption of a proton pump inhibiting agent into blood serum of a subject, comprising:

providing a solid pharmaceutical composition for administration to the subject, the composition comprising the proton pump inhibiting agent and a buffering agent; and

administering the pharmaceutical composition to the subject's stomach whereby the composition contacts gastric fluid of the stomach and increases the absorption of the proton pump inhibiting agent into the blood serum in an amount greater than the absorption of the proton pump inhibiting agent in the absence of the buffering agent;

wherein the buffering agent is in an amount sufficient to increase gastric fluid pH of the stomach to a pH that inhibits acid degradation of the proton pump inhibiting agent in the gastric fluid so as to provide a measurable serum concentration upon pharmacokinetic testing.

2. The method of claim 1, wherein the composition is administered in an amount to achieve a measurable serum concentration of the proton pump inhibiting agent greater than about 0.15  $\mu\text{g/ml}$  within about 15 minutes after ingestion of the composition.

3. The method of claim 1, wherein the composition is administered in an amount to achieve a measurable serum concentration of the proton pump inhibiting agent greater than about 0.15  $\mu\text{g/ml}$  from about 15 minutes to about 1 hour after ingestion of the composition.

4. The method of claim 1, wherein the composition is administered in an amount to achieve a measurable serum concentration of the proton pump inhibiting agent greater than about 0.15  $\mu\text{g/ml}$  from about 15 minutes to about 1.5 hours after ingestion of the composition.

- 5            5.        The method of claim 1, wherein the composition is administered in an amount to achieve a measurable serum concentration of the proton pump inhibiting agent greater than about 0.1  $\mu\text{g/ml}$  within about 15 minutes after ingestion of the composition.
6.        The method of claim 1, wherein the composition is administered in an amount to achieve a measurable serum concentration of the proton pump inhibiting agent greater than about 10    0.1  $\mu\text{g/ml}$  from about 15 minutes to about 1.5 hours after ingestion of the composition.
7.        The method of claim 1, wherein the composition is administered via a route selected from the group consisting of oral, nasogastric, and stomach tube.
8.        The method of claim 1, wherein the pharmaceutical composition is in a form selected from the group consisting of a tablet, capsule, powder, suspension tablet, effervescent 15    tablet or capsule, granules, and a liquid created by mixing any of the foregoing with an aqueous medium.
9.        The method of claim 1, wherein the proton pump inhibiting agent is enteric coated.
10.      The method of claim 1, wherein the amount of the proton pump inhibiting agent 20    absorbed into the blood serum is therapeutically effective in treating an acid related gastrointestinal condition selected from the group consisting of duodenal ulcer disease, gastric ulcer disease, gastroesophageal reflux disease, erosive esophagitis, poorly responsive symptomatic gastroesophageal reflux disease, pathological gastrointestinal hypersecretory disease, Zollinger Ellison Syndrome, and acid dyspepsia.
- 25           11.      The method of claim 1, wherein the proton pump inhibiting agent is selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole, or an enantiomer, isomer, derivative, free base, or salt thereof.

- 5           12.    The method of claim 1, wherein the amount of the proton pump inhibiting agent is about 5 mg to about 300 mg.
13.    The method of claim 1, wherein the amount of the proton pump inhibiting agent is about 10 mg to about 100 mg.
14.    The method of claim 1, wherein the amount of the proton pump inhibiting agent is  
10   about 15 mg.
15.    The method of claim 1, wherein the amount of the proton pump inhibiting agent is about 20 mg.
- 
16.    The method of claim 1, wherein the amount of the proton pump inhibiting agent is about 40 mg.
- 15          17.    The method of claim 1, wherein the amount of the buffering agent is about 0.1 mEq to about 2.5 mEq per mg of proton pump inhibiting agent.
18.    The method of claim 1, wherein the amount of the buffering agent is about 10 mEq to about 70 mEq.
- 19    The method of claim 1, wherein the amount of the buffering agent is at least 10  
20   mEq.
20.    The method of claim 1, wherein the amount of the buffering agent is about 20 mEq to about 40 mEq.
21.    The method of claim 1, wherein the buffering agent comprises a combination of calcium carbonate and sodium bicarbonate.
- 25          22.    The method of claim 1, wherein the buffering agent comprises a bicarbonate salt of a Group IA metal.

5           23.    The method of claim 1, wherein the buffering agent comprises at least one of magnesium hydroxide, magnesium lactate, magnesium gluconate, magnesium oxide, magnesium carbonate, or magnesium silicate.

          24.    The method of claim 1, wherein the buffering agent comprises at least one of calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium  
10   lactate, calcium carbonate, calcium bicarbonate, calcium gluconate, or other calcium salts.

          25.    The method of claim 1, wherein the buffering agent comprises sodium bicarbonate.

          26.    The method of claim 25, wherein the sodium bicarbonate is in an amount from about 250 mg to about 4000 mg.

15           27.    The method of claim 25, wherein the sodium bicarbonate is in an amount from about 1000 mg to about 1680 mg

          28.    The method of claim 25, wherein the sodium bicarbonate is in an amount of at least about 800 mg.

          29.    The method of claim 1, wherein the buffering agent comprises calcium carbonate.

20           30.    The method of claim 29, wherein the calcium carbonate is in an amount from about 250 mg to about 4000 mg.

          31.    The method of claim 29, wherein the calcium carbonate is in an amount from about 500 mg to about 1000 mg.

5            32.    The method of claim 29, wherein the calcium carbonate is in an amount of at least about 800 mg.

          33.    The method of claim 1, wherein the composition is in a dosage form selected from the group consisting of a tablet, powder, suspension tablet, chewable tablet, capsule, effervescent powder, effervescent tablet, pellet, and granule.

10           34.    The method of claim 1, wherein the composition further comprises a disintegrant, flow aid, lubricant, adjuvant, excipient, colorant, diluent, moistening agent, preservative, or a pharmaceutically compatible carrier.

          35.    The method of claim 1, wherein the composition further comprises a flavoring agent comprising aspartame, chocolate, root beer, peppermint, spearmint, or watermelon, and  
15 combinations of any of the foregoing.

          36.    The method of claim 1, wherein the composition is administered once or twice a day.

5           37.    A method of treating an acid related gastrointestinal disorder in a subject in need thereof, comprising:

          orally administering to the subject a solid pharmaceutical composition comprising a proton pump inhibiting agent and a buffering agent;

          wherein the buffering agent is in an amount sufficient to increase stomach content pH to  
10   a pH that inhibits acid degradation of the proton pump inhibiting agent in the stomach and to allow absorption of the proton pump inhibiting agent into blood serum of the subject in an amount greater than the absorption of the proton pump inhibiting agent in the absence of the buffering agent; and wherein the amount of proton pump inhibiting agent absorbed into the blood serum is therapeutically effective in treating the disorder.

15           38.    The method of claim 37, wherein the composition is administered in an amount to achieve a measurable serum concentration of the proton pump inhibiting agent greater than about 0.15 µg/ml within about 15 minutes after administration of the composition.

          39.    The method of claim 37, wherein the composition is administered in an amount to achieve a measurable serum concentration of the proton pump inhibiting agent greater than about  
20   0.15 µg/ml from about 15 minutes to about 1 hour after administration of the composition.

          40.    The method of claim 37, wherein the composition is administered in an amount to achieve a measurable serum concentration of the proton pump inhibiting agent greater than about 0.15 µg/ml from about 15 minutes to about 1.5 hours after administration of the composition.

          41.    The method of claim 37, wherein the composition is administered in an amount to  
25   achieve a measurable serum concentration of the proton pump inhibiting agent greater than about 0.1 µg/ml within about 15 minutes after administration of the composition.

5           42.    The method of claim 37, wherein the composition is administered in an amount to achieve a measurable serum concentration of the proton pump inhibiting agent greater than about 0.1 µg/ml from about 15 minutes to about 1 hour after administration of the composition.

          43.    The method of claim 37, wherein the subject is fasting.

          44.    The method of claim 37, wherein the pharmaceutical composition is in a form  
10   selected from the group consisting of a tablet, capsule, powder, suspension tablet, effervescent tablet or capsule, granules, and a liquid created by mixing any of the foregoing with an aqueous medium.

          45.    The method of claim 37, wherein the proton pump inhibiting agent is enteric coated.

15           46.    The method of claim 37, wherein the composition is administered via a route selected from the group consisting of oral, nasogastric, and stomach tube.

          47.    The method of claim 37, wherein the proton pump inhibiting agent is selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole, or an enantiomer, isomer, derivative, free base, or salt thereof.

20           48.    The method of claim 37, wherein the amount of the proton pump inhibiting agent is in an amount of about 5 mg to about 300 mg.

          49.    The method of claim 37, wherein the amount of the proton pump inhibiting agent is about 10 mg to about 100 mg.

          50.    The method of claim 37, wherein the amount of the proton pump inhibiting agent  
25   is about 15 mg.

          51.    The method of claim 37, wherein the amount of the proton pump inhibiting agent is about 20 mg.



5            52.    The method of claim 37, wherein the amount of the proton pump inhibiting agent is about 40 mg.

             53.    The method of claim 37, wherein the buffering agent is about 0.1 mEq to about 2.5 mEq per mg of proton pump inhibiting agent.

             54.    The method of claim 37, wherein the amount of the buffering agent is about 10  
10    mEq to about 70 mEq.

             55    The method of claim 37, wherein the amount of the buffering agent is at least 10  
mEq.

             56.    The method of claim 37, wherein the amount of the buffering agent is about 20  
mEq to about 40 mEq.

15           57.    The method of claim 37, wherein the buffering agent comprises a combination of calcium carbonate and sodium bicarbonate.

             58.    The method of claim 37, wherein the buffering agent comprises a bicarbonate salt of a Group IA metal.

             59.    The method of claim 37, wherein the buffering agent comprises at least one of  
20    magnesium hydroxide, magnesium lactate, magnesium gluconate, magnesium oxide, magnesium carbonate, or magnesium silicate.

             60.    The method of claim 37, wherein the buffering agent comprises at least one of calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, calcium gluconate, or other calcium salts.

25           61.    The method of claim 37, wherein the buffering agent comprises sodium bicarbonate.

- 5            62.    The method of claim 61, wherein the sodium bicarbonate is in an amount from  
about 250 mg to about 4000 mg.
63.    The method of claim 61, wherein the sodium bicarbonate is in an amount from  
about 1000 mg to about 1680 mg
64.    The method of claim 61, wherein the sodium bicarbonate is in an amount of at  
10    least about 800 mg.
65.    The method of claim 37, wherein the buffering agent comprises calcium  
carbonate.
66.    The method of claim 65, wherein the calcium carbonate is in an amount from  
about 250 mg to about 4000 mg.
- 15           67.    The method of claim 65, wherein the calcium carbonate is in an amount from  
about 500 mg to about 1000 mg.
68.    The method of claim 65, wherein the calcium carbonate is in an amount of at least  
about 800 mg.
69.    The method of claim 37, wherein the composition is in a dosage form selected  
20    from the group consisting of a tablet, powder, suspension tablet, chewable tablet, capsule,  
effervescent powder, effervescent tablet, pellet, and granule.
70.    The method of claim 37, wherein the composition further comprises a  
disintegrant, flow aid, lubricant, adjuvant, excipient, colorant, diluent, moistening agent,  
preservative, or a pharmaceutically compatible carrier.

5           71.    The method of claim 37, wherein the subject is an adult human.

          72.    The method of claim 37, wherein the disorder is selected from the group  
consisting of duodenal ulcer disease, gastric ulcer disease, gastroesophageal reflux disease,  
erosive esophagitis, poorly responsive symptomatic gastroesophageal reflux disease,  
pathological gastrointestinal hypersecretory disease, Zollinger Ellison Syndrome, and acid  
10   dyspepsia.

          73.    The method of claim 37, wherein the composition further comprising a flavoring  
agent comprising aspartame, chocolate, root beer, peppermint, spearmint, or watermelon, and  
combinations of any of the foregoing.

          74.    The method of claim 37, wherein the composition is administered once or twice a  
15   day.

5           75.    A method of treating an acid related gastrointestinal disorder in a subject in need thereof, comprising:

              orally administering to the subject a pharmaceutical composition in an oral dosage form for immediate release into an absorption pool having a highly acidic pH, the composition comprising a proton pump inhibiting agent and a buffering agent;

10           wherein the buffering agent is in an amount sufficient to increase the pH of the absorption pool of the subject to a pH that inhibits acid degradation of the proton pump inhibiting agent and to allow absorption of the proton pump inhibiting agent from the absorption pool into blood serum of the subject in an amount greater than the absorption of the proton pump inhibiting agent in the absence of the buffering agent; and

15           wherein the proton pump inhibiting agent is in an amount sufficient to achieve a measurable serum concentration in the blood serum of the subject after oral administration to the subject.

              76.    The method of claim 75, wherein the composition is administered in an amount to achieve a measurable serum concentration of the proton pump inhibiting agent greater than about  
20   0.15 µg/ml within about 15 minutes after administration of the composition.

              77.    The method of claim 75, wherein the composition is administered in an amount to achieve a measurable serum concentration of the proton pump inhibiting agent greater than about 0.15 µg/ml from about 15 minutes to about 1 hour after administration of the composition.

              78.    The method of claim 75, wherein the composition is administered in an amount to  
25   achieve a measurable serum concentration of the proton pump inhibiting agent greater than about 0.15 µg/ml from about 5 minutes to about 1.5 hours after administration of the composition.

- 5            79.    The method of claim 75, wherein the composition is administered in an amount to achieve a measurable serum concentration of the proton pump inhibiting agent greater than about 0.1 µg/ml within about 15 minutes after administration of the composition.
80.    The method of claim 75, wherein the composition is administered in an amount to achieve a measurable serum concentration of the proton pump inhibiting agent greater than about 10    0.1 µg/ml from about 15 minutes to about 1.5 hours after administration of the composition.
81.    The method of claim 75, wherein the subject is fasting.
82.    The method of claim 75, wherein the pharmaceutical composition is in a form selected from the group consisting of a tablet, capsule, powder, suspension tablet, effervescent tablet or capsule, granules, and a liquid created by mixing any of the foregoing with an aqueous 15    medium.
83.    The method of claim 75, wherein the proton pump inhibiting agent is enteric coated.
84.    The method of claim 75, wherein the composition is administered via a route selected from the group consisting of oral, nasogastric, and stomach tube.
- 20           85.    The method of claim 75, wherein the proton pump inhibiting agent is selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole, or an enantiomer, isomer, derivative, free base, or salt thereof.
86.    The method of claim 75, wherein the amount of the proton pump inhibiting agent is in an amount of about 5 mg to about 300 mg.
- 25           87.    The method of claim 75, wherein the amount of the proton pump inhibiting agent is about 10 mg to about 100 mg.

- 5            88.    The method of claim 75, wherein the amount of the proton pump inhibiting agent  
is about 15 mg.
89.    The method of claim 75, wherein the amount of the proton pump inhibiting agent  
is about 20 mg.
90.    The method of claim 75, wherein the amount of the proton pump inhibiting agent  
10 is about 40 mg.
91.    The method of claim 75, wherein the buffering agent is about 0.1 mEq to about  
2.5 mEq per mg of proton pump inhibiting agent.
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92.    The method of claim 75, wherein the amount of the buffering agent is about 10  
mEq to about 70 mEq.
- 15           93    The method of claim 75, wherein the amount of the buffering agent is at least 10  
mEq.
94.    The method of claim 75, wherein the amount of the buffering agent is about 20  
mEq to about 40 mEq.
95.    The method of claim 75, wherein the buffering agent comprises a combination of  
20 calcium carbonate and sodium bicarbonate.
96.    The method of claim 75, wherein the buffering agent comprises a bicarbonate salt  
of a Group IA metal.
97.    The method of claim 75, wherein the buffering agent comprises at least one of  
magnesium hydroxide, magnesium lactate, magnesium gluconate, magnesium oxide, magnesium  
25 carbonate, or magnesium silicate.

5            98.    The method of claim 75, wherein the buffering agent comprises at least one of calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, calcium gluconate, or other calcium salts.

          99.    The method of claim 75, wherein the buffering agent comprises sodium bicarbonate.

10           100.   The method of claim 99, wherein the sodium bicarbonate is in an amount from about 250 mg to about 4000 mg.

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          101.   The method of claim 99, wherein the sodium bicarbonate is in an amount from about 1000 mg to about 1680 mg

15           102.   The method of claim 99, wherein the sodium bicarbonate is in an amount of at least about 800 mg.

          103.   The method of claim 75, wherein the buffering agent comprises calcium carbonate.

          104.   The method of claim 103, wherein the calcium carbonate is in an amount from about 250 mg to about 4000 mg.

20           105.   The method of claim 103, wherein the calcium carbonate is in an amount from about 500 mg to about 1000 mg.

          106.   The method of claim 103, wherein the calcium carbonate is in an amount of at least about 800 mg.

5           107.   The method of claim 75, wherein the composition is in a dosage form selected from the group consisting of a tablet, powder, suspension tablet, chewable tablet, capsule, effervescent powder, effervescent tablet, pellet, and granule.

          108.   The method of claim 75, wherein the composition further comprises a disintegrant, flow aid, lubricant, adjuvant, excipient, colorant, diluent, moistening agent,  
10   preservative, or a pharmaceutically compatible carrier.

          109.   The method of claim 75, wherein the subject is an adult human.

          110.   The method of claim 75, wherein the disorder is selected from the group consisting of duodenal ulcer disease, gastric ulcer disease, gastroesophageal reflux disease, erosive esophagitis, poorly responsive symptomatic gastroesophageal reflux disease,  
15   pathological gastrointestinal hypersecretory disease, Zollinger Ellison Syndrome, and acid dyspepsia.

          111.   The method of claim 75, wherein the composition further comprising a flavoring agent comprising aspartame, chocolate, root beer, peppermint, spearmint, or watermelon, and combinations of any of the foregoing.

20           112.   The method of claim 75, wherein the composition is administered once or twice a day.



5           113. A method of making a pharmaceutical composition for oral administration to a subject, providing immediate release of a proton pump inhibiting agent and a buffering agent into an absorption pool having a highly acidic pH, comprising:

          admixing the proton pump inhibiting agent and the buffering agent;

          wherein the buffering agent is in an amount sufficient to increase the pH of the  
10   absorption pool of the subject to a pH that inhibits acid degradation of the proton pump inhibiting agent and to allow absorption of the proton pump inhibiting agent from the absorption pool into blood serum of the subject in an amount greater than the absorption of the proton pump inhibiting agent in the absence of the buffering agent; and

          wherein the proton pump inhibiting agent is in an amount sufficient to achieve a  
15   measurable serum concentration in the blood serum of the subject after oral administration to the subject.

          114. The method of claim 113, wherein the amount of buffering agent achieves a measurable serum concentration of the proton pump inhibiting agent greater than about 0.15  $\mu\text{g/ml}$  within about 15 minutes after administration of the composition.

20           115. The method of claim 113, wherein the amount of buffering agent achieves a measurable serum concentration of the proton pump inhibiting agent greater than about 0.15  $\mu\text{g/ml}$  from about 15 minutes to about 1 hour after administration of the composition.

          116. The method of claim 113, wherein the amount of buffering agent achieves a measurable serum concentration of the proton pump inhibiting agent greater than about 0.15  
25    $\mu\text{g/ml}$  from about 15 minutes to about 1.5 hours after administration of the composition.

5           117. The method of claim 113, wherein the amount of buffering agent achieves a measurable serum concentration of the proton pump inhibiting agent greater than about 0.1  $\mu\text{g/ml}$  within about 15 minutes after administration of the composition.

          118. The method of claim 113, wherein the amount of buffering agent achieves a measurable serum concentration of the proton pump inhibiting agent greater than about 0.1  $\mu\text{g/ml}$  from about 15 minutes to about 1.5 hours after administration of the composition.

10           119. The method of claim 113, wherein the composition is administered via a route selected from the group consisting of oral, nasogastric, and stomach tube.

          120. The method of claim 113, wherein the pharmaceutical composition is in a form selected from the group consisting of a tablet, capsule, powder, suspension tablet, effervescent tablet or capsule, granules, and a liquid created by mixing any of the foregoing with an aqueous medium.

          121. The method of claim 113, wherein the proton pump inhibiting agent is enteric coated.

          122. The method of claim 113, wherein the proton pump inhibiting agent is acid sensitive.

          123. The method of claim 113, wherein the proton pump inhibiting agent is selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole, or an enantiomer, isomer, derivative, free base, or salt thereof.

          124. The method of claim 113, wherein the amount of the proton pump inhibiting agent is about 5 mg to about 300 mg.

          125. The method of claim 113, wherein the amount of the proton pump inhibiting agent is about 10 mg to about 100 mg.

5           126. The method of claim 113, wherein the amount of the proton pump inhibiting agent is about 15 mg.

          127. The method of claim 113, wherein the amount of the proton pump inhibiting agent is about 20 mg.

          128. The method of claim 113, wherein the amount of the proton pump inhibiting  
10 agent is about 40 mg.

          129. The method of claim 113, wherein the amount of the buffering agent is about 0.1 mEq to about 2.5 mEq per mg of proton pump inhibiting agent.

          130. The method of claim 113, wherein the amount of the buffering agent is about 10 mEq to about 70 mEq.

15           131. The method of claim 113, wherein the amount of the buffering agent is at least 10 mEq.

          132. The method of claim 113, wherein the amount of the buffering agent is about 20 mEq to about 40 mEq.

          133. The method of claim 113, wherein the buffering agent comprises a combination  
20 of calcium carbonate and sodium bicarbonate.

          134. The method of claim 113, wherein the buffering agent comprises a bicarbonate salt of a Group IA metal.

          135. The method of claim 113, wherein the buffering agent comprises at least one of  
magnesium hydroxide, magnesium lactate, magnesium gluconate, magnesium oxide, magnesium  
25 carbonate, or magnesium silicate.

5           136. The method of claim 113, wherein the buffering agent comprises at least one of calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, calcium gluconate, or other calcium salts.

          137. The method of claim 113, wherein the buffering agent comprises sodium bicarbonate.

10           138. The method of claim 137, wherein the sodium bicarbonate is in an amount from about 250 mg to about 4000 mg.

          139. The method of claim 137, wherein the sodium bicarbonate is in an amount from about 1000 mg to about 1680 mg

          140. The method of claim 137, wherein the sodium bicarbonate is in an amount of at  
15 least about 800 mg.

          141. The method of claim 113, wherein the buffering agent comprises calcium carbonate.

          142. The method of claim 141, wherein the calcium carbonate is in an amount from about 250 mg to about 4000 mg.

20           143. The method of claim 141, wherein the calcium carbonate is in an amount from about 500 mg to about 1000 mg.

          144. The method of claim 141, wherein the calcium carbonate is in an amount of at least about 800 mg.

- 5           145.   The method of claim 113, wherein the composition is in a dosage form selected from the group consisting of a tablet, powder, suspension tablet, chewable tablet, capsule, effervescent powder, effervescent tablet, pellet, and granule.
146.   The method of claim 113, wherein the composition further comprises a disintegrant, flow aid, lubricant, adjuvant, excipient, colorant, diluent, moistening agent,  
10   preservative, or a pharmaceutically compatible carrier.
147.   The method of claim 113, wherein the subject has an acid related gastrointestinal disorder.
148.   The method of claim 147, wherein the disorder is selected from the group consisting of duodenal ulcer disease, gastric ulcer disease, gastroesophageal reflux disease,  
15   erosive esophagitis, poorly responsive symptomatic gastroesophageal reflux disease, pathological gastrointestinal hypersecretory disease, Zollinger Ellison Syndrome, and acid dyspepsia.
149.   The method of claim 113, wherein the composition further comprising a flavoring agent comprising aspartame, chocolate, root beer, peppermint, spearmint, or watermelon, and  
20   combinations of any of the foregoing.
150.   The method of claim 113, wherein the composition is administered once or twice a day.